Recl. Trav. Chim. Pays-Bas **114**, 91–96 (1995)
SSDI 0165-0513(95)00006-2

0165-0513/95/03091-06$9.50

Synthesis of chiral sulfines by oxidation of dithio esters

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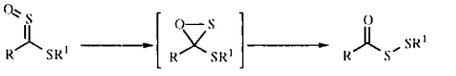
(Received September 12, 1994)

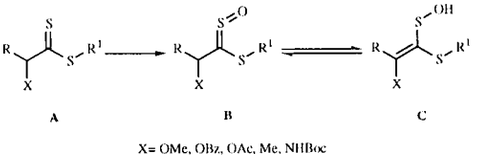
Abstract. The synthesis of sulfines (thione oxides) (**2**, **10** and **17**) derived from three chiral dithio esters (**1**, **8** and **16**) bearing a hydrogen at the α-carbon atom is described. The sulfine bearing an amido group at C-α (**2**), does not racemize and proved to be stable over a long period. When C-α in the sulfine (**10**) bears an acetoxy group the optical activity remained unchanged for a period of two months; after longer storage a rearrangement to a mixture of dithioperoxy ester **12** and *S*-methyl ester **11** took place. With an alkyl group at C-α, the sulfine **17** undergoes a fast racemization and rearranges slowly to a mixture of *S*-ethyl ester **14**, dithioperoxy ester **18** and *S*-vinyl thiosulfinate **19**.

Introduction

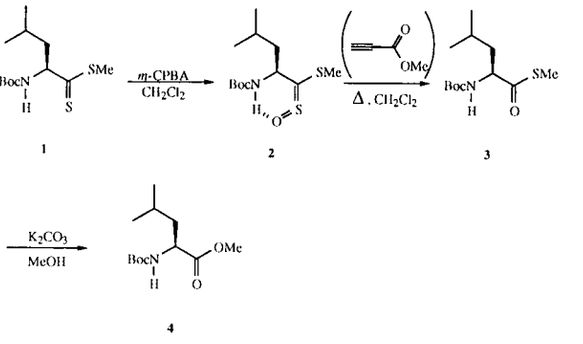
Oxidation of thiocarbonyl-containing compounds is the most versatile method for the preparation of sulfines (thione oxides). A large variety of sulfines is accessible by oxidation using organic peracids[1–4]. It was assumed that this method could not be extended to thiocarbonyl compounds bearing a hydrogen at the α-carbon atom[1,2,5]. Although a limited number of examples challenging this hypothesis have been reported[6–8], it was not until recently that *Metzner* et al.[9–12] showed that aliphatic dithio esters can readily be oxidized with 3-chloroperbenzoic acid to the corresponding *thiono* oxides.
These aliphatic sulfines are thermally rather unstable due to a rearrangement to dithioperoxy esters. The mechanism for this reaction, proposed by *Metzner* et al.[9–12], is shown in Scheme 1.
With the aim of obtaining information about the tautomeric interconversion of aliphatic sulfines into vinylsulfenic acids (**B** → **C**, Scheme 2), some chiral sulfines bearing a hydrogen atom at C-α were prepared and the chiral integrity of the stereogenic center at C-α was studied.



Scheme 1.



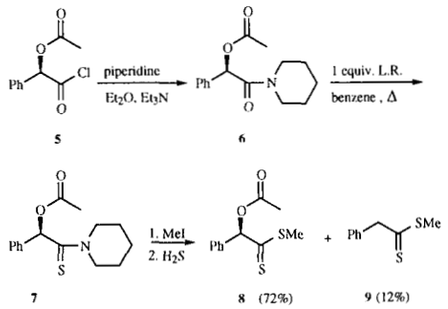
Scheme 2.



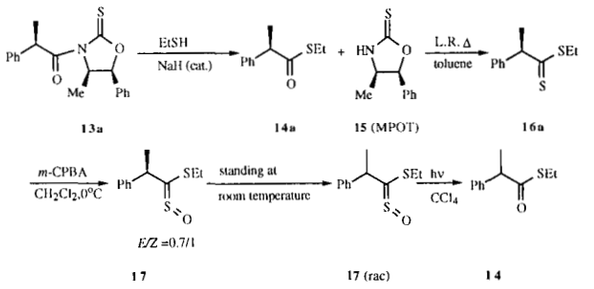
Scheme 3.

Results and discussion

In general, it may be expected that substitution of an α-hydrogen atom by a hetero-atom will influence the tautomerization of sulfines. In this context we synthesized chiral sulfines bearing different substituents at C-α. The first substrate for the synthesis of an α-chiral sulfine is L-leucine. The amino acid was converted into a dithio ester using Lawesson's reagent, which is a known racemization-free thionation agent[13–15]. Oxidation of amido dithio ester **1** with 3-chloroperbenzoic acid gave the desired optically active sulfine **2** as a single isomer in 63% yield (Scheme 3). Unlike the aliphatic sulfines described by *Metzner*, which were very unstable and gave a complete rearrangement after a few days, sulfine **2** is stable for a few years and retained its initial optical rotation. Most likely, sulfine **2** is present as its *E* isomer, which is stabilized by intramolecular hydrogen bonding as indicated in the formula. It should be noted that no trace of the corresponding dithioperoxy ester could be detected. On heating the sulfine **2** in dichloromethane in the presence of methyl propynoate[16] as a sulfenic-acid scavenger, *S*-methyl ester **3** was obtained instead of an addition product. *S*-Methyl ester **3** was converted into the corre-



Scheme 4.



Scheme 6.

sponding carboxylic ester by treatment with potassium carbonate in methanol; the optical rotation of this ester is comparable with the literature value ($[\alpha]_D^{25} - 8.34$, c 2.2 in CH_2Cl_2; $[\alpha]_D^{20} - 7.1$, c 2.0 in CH_2Cl_2[17]; $[\alpha]_D^{25} + 8.84$, c 1.91 in CH_2Cl_2[18] for the corresponding D-leucine analog of **4**). It is of interest to note that this loss of sulfur from sulfine **2** probably proceeds via an oxathiirane intermediate[19], however, this intermediate does not undergo rearrangement to a dithioperoxy ester (*cf.* Scheme 1).

Mandelic acid (α-hydroxy-phenylacetic acid) is an attractive optically active substrate for the synthesis of sulfines bearing an oxygen atom at C-α (Scheme 2, X=OMe). This chiral acid was methylated[20,21] and subsequently treated with thionyl chloride and reacted with ethanethiol in the presence of triethylamine to produce *S*-ethyl ethanethioate (**B**: R=Ph, X=OMe, R'=Et) in 83% yield. Unfortunately, treatment of this *S*-ethyl ester with Lawesson's reagent (L.R.) in toluene did not result in the formation of the desired dithio ester. Only unidentified products were obtained.

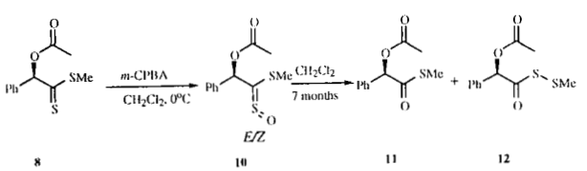
Confronted with this result we tried to obtain the dithio ester of mandelic acid via the route depicted in Scheme 4. Thus, acetylation of mandelic acid and subsequent conversion into amide **6** followed by treatment with Lawesson's reagent gave thioamide **7** in an overall yield of 50%. *S*-Methylation with methyl iodide led to an iminium salt which on reaction with hydrogen sulfide in ethanol gave the desired dithio ester **8** in 72% yield (calculated on **7**) and methyl phenylethanedithioate **9** as a by-product (12%). When a benzoyl group was used instead of an acetyl group, thionation of the corresponding amide did not give the corresponding thioamide. Oxidation of dithio ester **8** with 3-chloroperbenzoic acid in dichloromethane gave the desired sulfine **10** in 78% yield, as a mixture of *E* and *Z* isomers (ratio *E*/*Z* 0.9/1, $[\alpha]_D^{25} + 45.6$, c 4.7 in CH_2Cl_2, Scheme 5).

The thermal stability of sulfine **10** was then investigated. After storage for 2 months sulfine **10** gave the same optical rotation, indicating that no racemization had occurred. When stored in solution for 7 months, sulfine **10** gave a rearrangement to a 1/1 mixture of dithioperoxy ester **12** and *S*-methyl ester **11**, which were inseparable (Scheme 5). The mixture of **11** and **12** showed optical activity ($[\alpha]^4125_D - 27.4$, c 3.9 in CH_2Cl_2). Although the optical purity of the individual compounds has not been determined, this result suggests that racemization and accordingly tautomerization of **10**, **11** and **12** (*cf.* Scheme 2) is very slow.

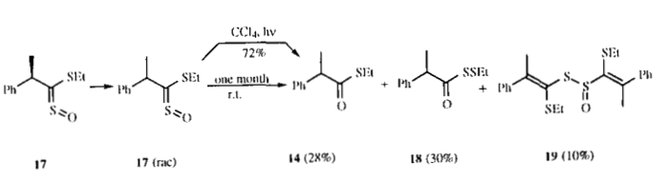
The third substrate is ethyl 2-phenyl-propanedithioate (**B**, R=Ph, X=Me, R'=Et). Racemic 2-phenylpropanoic acid was coupled with (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (MPOT) using dicyclohexylcarbodiimide (DCC). The diastereoisomeric mixture of amides **13a** and **13b** was conveniently separated by column chromatography[22,23]. The separated MPOT-diastereoisomer **13a** (d.e. > 95%, according to ^{1}H-NMR spectral analysis) was converted into the corresponding *S*-ethyl ester **14a** by treatment with ethanethiol in the presence of a catalytic amount of sodium hydride in 92% yield (Scheme 6, the absolute configuration in structures **14a** and **16a** is arbitrarily chosen). It is essential to use a catalytic amount of sodium hydride, because racemization of **14a** takes place when one equivalent of this base is used.

Treatment of *S*-ethyl ester **14a** with one equivalent of Lawesson's reagent in toluene produced dithio ester **16a** in 94% yield. This thionation is reported to be free of racemization[13,14,15]. As the conversion of **13a** into **14a** and that of **14a** into **16a** is not accompanied by racemization, the e.e. of **16a** is estimated to be more than 90%. Oxidation of optically active dithio ester **16a** with 3-chloroperbenzoic acid in dichloromethane resulted, after work-up and purification, in the isolation of **17**, which was obtained as an *E*/*Z* mixture (ratio 0.7/1, Scheme 6). The optical rotation of this sulfine, when measured immediately after its isolation, amounted to $[\alpha]_D^{25} + 0.072$ (c 13.95, $CHCl_3$) but disappeared completely after standing for 24 h. Furthermore, the *E*/*Z* ratio had then changed to 1/1. This loss of optical activity is most likely attributable to racemization by tautomeric equilibration via a vinylsulfenic acid as shown in Scheme 2. The sulfine structure of compound **17** was confirmed by irradiation[19,24], which led to extrusion of sulfur to give racemic *S*-ethyl ester **14** (Scheme 6). To investigate the stability of sulfine **17** further, it was dissolved in dichloromethane and stirred for about one month while protected from light. During this period rearrangement to dithioperoxy ester **18** took place (yield 30%). Two other products, *i.e.* *S*-ethyl ester **14** and *S*-[1-(ethylthio)-2-phenyl-1-propenyl]-1-ethylthio-2-phenyl-1-propenesulfinate **19**, were also isolated after this long period of standing (Scheme 7). The formation of thiosulfinate **19** can be explained by assuming a self-condensation of the vinylsulfenic acid intermediate **C**.

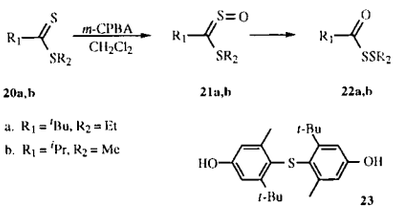
In order to shed more light on the formation of dithioperoxy esters from sulfines two simple aliphatic sulfines were prepared for rearrangement studies, namely *t*-butyl(ethyl-



Scheme 5.



Scheme 7.



Scheme 8.

thio)sulfine **21a** and *i*-propyl(methylthio)sulfine **21b**. Sulfine **21a** quantitatively rearranged to dithioperoxy ester **22a** on heating in dichloromethane for two days (Scheme 8). However, in the presence of radical scavenger **23**, heating in refluxing dichloromethane for the same period did not produce any of the rearranged product and the sulfine was recovered unchanged. Sulfine **21a** on standing at room temperature for a period of more than 6 months did not produce any rearranged product, only *E / Z* isomerization was observed.

Iso-propyl(methylthio)sulfine **21b** dissolved in dichloromethane quantitatively rearranged during standing for 24 h at room temperature to dithioperoxy ester **22b** (Scheme 8). Addition of radical scavenger **23** slowed down this process considerably, such that complete rearrangement took 4 days (^{1}H-NMR spectra taken during this period showed also *E / Z* isomerization of **21b** to a ratio of 1/1).

The results described above suggest that the rearrangement proceeds via a radical mechanism. Support for this proposal is obtained from *Murai*[25] et al's claim that the formation of the selenolothiol ester R–C(=O)S–SePh, during the oxidation of R–C(=S)SePh to the corresponding *S*-oxide R–C(=SO)SePh, takes place via a radical intermediate, which was not further specified. A conversion of the sulfine R–C(=SO)SePh into selenolothiol ester R–C(=O)S–SePh was not observed. It was suggested that in this rearrangement 3-chloroperbenzoic acid plays the role of a radical initiator. Additional evidence for a radical intermediate was provided by *Carlsen* et al.[26], who proposed a biradical intermediate arising from an initially formed oxathiirane to explain the formation of *O*- and *S*-phenyl benzothioate, when diphenylsulfine was irradiated at 85K. This biradical intermediate is formed from the oxathiirane intermediate.

The results described in this paper indicate that the stability of the sulfine depends strongly on the substituents at C-α. A dithio ester-derived sulfine bearing an alkyl group at C-α undergoes a fast racemization via vinylsulfenic acid **C**. On standing, the unstable sulfine rearranges slowly to a mixture of thio ester, dithioperoxy ester and a self-condensate of the vinylsulfenic acid (Scheme 7). When C-α in the sulfine bears an acetoxy group, the rearrangement to a mixture of dithioperoxy ester and thio ester still took place, but no evidence for racemization was obtained.

With an amido group at C-α, the sulfine is stabilized by intramolecular hydrogen bonding and does not racemize, even after several years the compound maintained its stereochemical integrity. No trace of the corresponding dithioperoxy esters was found.

Experimental

IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer. The 90-MHz ^{1}H-NMR spectra were recorded on a Varian EM-390 spectrometer (Me_4Si as internal standard) and for the 100-MHz ^{1}H-NMR spectra a Bruker AC 100 spectrometer (Me_4Si as internal standard) was used. For the ^{13}C-NMR spectra a Bruker AC 100 spectrometer ($CDCl_3$ as internal standard) was used. For mass spectra a double focussing VG7070E mass spectrometer was used. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. Dichloromethane was distilled from P_2O_5. THF was distilled from $LiAlH_4$. Diethyl ether was distilled from NaH. Petroleum-ether (60–80°C) was distilled from NaH. Hexane was distilled from NaH. Acetonitrile was distilled from P_2O_5. Ethyl acetate was distilled from K_2CO_3. All syntheses were performed in an argon atmosphere. *n*-Butyllithium was used as a standard solution of 1.6 M in hexane. GLC was conducted with a Hewlett-Packard HP 5890 gas chromatograph, using a capillary column (25 m) of HP-1, and nitrogen (2 ml/min, 0.5 atm) as the carrier gas. Thin layer chromatography (TLC) was carried out on Merck precoated silica gel 60 F254 plates (0.25 mm) using the eluents indicated. Spots were visualized with UV and spraying with 5% H_2SO_4 solution in ethanol followed by charring at 140°C for 15 min. Flash chromatography was carried out at a pressure of *ca.* 1.5 bar, a column length of 15–25 cm and a column diameter of 1–4 cm, using Merck Kieselgel 60H, unless stated otherwise.

L-N-tert-*Butoxycarbonyl-dithioleucine methyl ester thione oxide* (**2**)

A solution of 3-chloroperbenzoic acid (0.544 g, 70–75% pure, 1.0 equiv.) in dichloromethane (20 ml) was dried on magnesium sulfate and added to a stirred solution of L-*N*-Boc-dithioleucine methyl ester (**1**, 0.655 g, 2.48 mmol) [synthesized according to Lawesson[23]] in dichloromethane (25 ml) while kept at 0°C. The reaction mixture was stirred for an additional 20 min, while following the progress of the reaction by TLC. The reaction mixture was then subsequently washed with a saturated aqueous sodium pyrosulfite solution (30 ml) and a saturated potassium hydrogen carbonate solution (3×30 ml). The organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 60 H, petroleum-ether (60–80°C)/ethyl acetate, 3/1, v/v), to give 0.438 g (63%) of sulfine **2** as a white solid, m.p. 63–64°C, $[\alpha]_D^{25}$ +68.7 (c 7.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 0.95 (d, *J* 5Hz, 6H, $(CH_3)_2CH$), 1.45 (s, 9H, ^{t}Bu–O–C=O), 1.5–1.8 (m, 3H, $(CH_3)_2CH-CH_2-$), 2.37 (s, 3H, SMe),. 4.51 (m, 1H, CH–N), 4.9 (broad d, 1H, NH) ppm. IR (CCl_4,): ν 3438 (s, N–H), 2920 (m), 1720 (s, N–C=O), 1485 (s), 1365 (m), 1160 (s, C=S=O), 1060 (s, C=S=O), 1045 (ms), 1015 (ms), 910 (vs) cm^{-1}. MS (CI) *m / z:* 294 (M^++1), 57 ($^tBu^+$). CI/HRMS *m / z:* 294.12006 ±0.00088 [calcd. for $C_{12}H_{24}NO_3S_2$ (M^++1): 294.11976].

L-N-(tert *Butoxycarbonyl)-thioleucine* S-*methyl ester* (**3**)

A solution of sulfine **2** (0.330 g, 1.18 mmol) in dichloromethane (25 ml) protected from light, was stirred for 1 month. Then the volatiles were evaporated *in vacuo* and the residue was purified by column chromatography (silica gel 60H, petroleum-ether (60–80°C)/ethyl acetate, 3:1, v/v) to give 0.200 g (61%) of **3** as a white solid, m.p. 94°C; $[\alpha]_D^{25}$ −50.8 (c 7.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 0.95 (d, 6H, *J* 5Hz, $(CH_3)_2CH$), 1.45 (s, 9H, ^{t}Bu–O–C=O), 1.5–1.9 (m, 3H, $(CH_3)_2CH-CH_2-$), 2.45 (s, 3H, SMe), 4.9 (broad d, 1H, NH), 5.51 (m, 1H, CH–N) ppm. IR (CCl_4): ν 3436 (s), 2920 (m), 1717 (s, N–C=O), 1690 (s, S–C=O), 1480 (s), 1370 (m), 1170 (s), 1045 (ms), 1015 ms), 960 (vs) cm^{-1}. MS (CI) *m / z:* 262 (M^++1), 186 (M^+ −O=C–S–CH_3), 57 ($^tBu^+$). CI/HRMS *m / z:* 262.14767 ±0.00088 [calcd. for $C_{12}H_{24}NO_3S$ (M^++1): 262.14769].

L-N-(tert *Butoxycarbonyl)-leucine methyl ester* (**4**)

A solution of *S*-methyl ester **3** (0.200 g, 0.77 mmol) and potassium carbonate (1.53 g, 1.54 mmol) in methanol (50 ml) was heated under reflux for 5 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and extracted with a saturated ammonium chloride solution (3×30 ml). The organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 60H, petroleum-ether (60–80°C)/ethyl acetate, 4/1, v/v) to give 0.110 g (58%) of **4** as an oil. $[\alpha]_D^{25}$ −8.31 (c 2.2, CH_2Cl_2). Spectral data of the ester thus obtained are in excellent agreement with those of the ester obtained as described in the literature[17].

(R)-α-*Acetoxy-phenylethanepiperidamide* (**6**)

A solution of piperidine (4.9 ml, 4.26 g, 50 mmol) in diethyl ether (20 ml) was gradually added to a cooled (0°C) solution of α-acetoxyphenylacetyl chloride **5**[27] (5 g, 23.5 mmol) in diethyl ether (100 ml). After stirring for 2 h, the white precipitate was removed by filtration, and the solids were washed with diethyl ether (3×25 ml). The combined organic layers were concentrated *in vacuo*. The crude

product was purified by crystallization from toluene/petroleum-ether (60–80°C) to give 6.13 g (88%) of **6** as white crystals, m.p.: 100–102°C. $[\alpha]_D^{25}$ −68.61 ($CHCl_3$, c 5.35). ^{1}H-NMR (in $CDCl_3$): δ 1.20–1.60 (broad s, 6H, N–CH_2–CH_2–CH_2–CH_2–), 2.0 (s, 3H, CH_3C=O), 3.2–3.5 (broad s, 4 H, –CH_2–N–CH_2–), 6.03 (s, 1H, Ph–CH), 7.20 (s, 5H, Ph) ppm. IR(KBr): ν 1740, 1440, 1230 (O–C=O), 1660 (N–C=O) cm^{-1}.

(R)-α-*Acetoxy-phenylethanethiopiperidamide* (**7**)

Lawesson's reagent [(4-$CH_3OC_6H_4PS_2)_2$, 4 g, 0.01 mol] was added in one portion to **6** (5.1 g, 0.02 mol) dissolved in benzene (50 ml). The reaction mixture was heated under reflux for 1 h and then concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 60H, petroleum-ether (60–80°C)/dichloromethane, 1/2, v/v) to give 2.87 g (53%) of thioamide **7** as a yellow oil. ^{1}H-NMR (in $CDCl_3$): δ 1.36–1.67 (broad s, 6H, N–CH_2–CH_2–CH_2–CH_2–), 2.0 (s, 3H, CH_3C=O), 3.40–3.65 (broad s, 2H, –CH_2–N–CH_2–), 4.0–4.2 (broad s, 2H, –CH_2–N–CH_2–), 6.43 (s, 1H, Ph–C–H), 7.0–7.2 (m, 3H, m and p Ph-H's), 7.27–7.40 (m, 2H, *o*-Ph-H's) ppm. IR (KBr): ν 1740 (C=O), 1440, 1280 (O–C=O), 1480, 1220 (N–C=S) cm^{-1} MS (EI) *m/z*: 277 (M^+), 128 (S=C–N–$(CH_2)_5^+$), 84 (N–$(CH_2)_5^+$), 43 (CH_3–C=O^+).

(R)-*S-Methyl α-acetoxy-phenylethanedithioate* (**8**)

Methyl iodide (1.30 ml, 2.92 g, 20.6 mmol) was added to a solution of thioamide **7** (1.42 g, 5.13 mmol) in THF (5 ml). After stirring for 12 h, the volatiles were evaporated *in vacuo*. The remaining syrup was dissolved in ethanol (50 ml) and cooled to 0°C with an ice bath and hydrogen sulfide was bubbled through for 1 h under slightly reduced pressure. The crude product was concentrated *in vacuo* and purified by column chromatography (silica gel 60H, petroleum-ether (60–80°C)/ethyl acetate, 6/1, v/v) to give two products; *viz.* 0.89 g (72%) of **8**, $[\alpha]_D^{25}$ − 44.02 ($CHCl_3$, c 5.65) and *S*-methyl phenylethanedithioate (**9**), 0.110 g (12%).
Spectral data of **8**. ^{1}H-NMR (in $CDCl_3$): δ 2.23 (s, 3H, CH_3C=O), 2.6 (s, 3H, S–CH_3), 6.53 (s, 1H, Ph–CH–C=S), 7.1–7.57 (m, 5H, Ph) ppm. IR(KBr): ν 1750 (C=O), 1418 (O–C=O), 1370 (O–C=O), 1220 (O–C=O), 1210 (S–C=S), 1130 (S–C=S) cm^{-1}. MS (EI) *m/z*: 240 (M^+), 181 (M^+ –O–C(=O)–CH_3), 149 (M^+ –CH_3–S–C=S).
Spectral data of **9**. ^{1}H-NMR ($CDCl_3$): δ 2.43 (s, 3H, SCH_3), 4.27 (s, 2H, Ph–CH_2–C=S), 7.16–7.42 (m, 5H, Ar) ppm. IR (CCl_4): ν 3020–2880, 1950–1670 (Ar), 1210, 1130 (C=S) cm^{-1}.

E- *And* Z-α-*(acetoxybenzyl)(methylthio)sulfine* (**10**)

Starting from dithio ester **8** (2.28 g, 9.5 mmol) and *m*-CPBA (2.2 g, 1.0 equiv., 70–75% pure, 95 mmol) sulfine **10** was synthesized according to the procedure used for sulfine **2**. The crude product was purified by column chromatography (silica gel 60, petroleum-ether (60–80°C)/ethyl acetate, 3/1, v/v), 1.90 g (78%) of sulfine **10**, as an oil, in an *E/Z* ratio of 0.9/1. $[\alpha]_D^{25}$ +45.64 (CH_2Cl_2, c 4.7; $[\alpha]_D^{25}$ + 50.3 (CH_2Cl_2, c 4.5) two months later, *E/Z* ratio 1/1. ^{1}H-NMR ($CDCl_3$) of the *Z* isomer (deduced from the spectra of the *E/Z* mixture): δ 2.17 (s, 3H, O=C–CH_3), 2.56 (s, 3H, S–CH_3), 6.7 (s, 1H, Ph–CH), 7.33–7.6 (m, 5H, Ph) ppm.
^{1}H-NMR ($CDCl_3$) of the *E* isomer (deduced from the spectra of the *E/Z* mixture): δ 2.19 (s, 3H, O=C–CH_3), 2.40 (s, 3H, S–CH_3), 7.23 (s, 1H, Ph–CH), 7.33–7.6 (m, 5H, Ph) ppm. IR(KBr): ν 1750 (s, O=C–O), 1210 (s, O=C–0), 1130 (s, O=S=C), 1020 (s, O=S=C) cm^{-1}. MS (EI) *m/z*:256 (M^+), 214 (M–S), 43 (CH_3C=O^+, 100%). EI/HRMS *m/z*: 256.0229 ±0.0010 [calcd. for $C_{11}H_{12}O_3S_2$ (M^+): 256.02279].

Rearrangement of sulfine **10**. A solution of sulfine **10** (0.512 g, 2.0 mmol in dichloromethane (25 ml) was kept at room temperature, protected from light, for 7 months and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel 60, petroleum-ether (60–80°C)/ethyl acetate, 3/1, v/v), to give 0.386 g (81%) of an inseparable mixture of *S*-methyl ester **11** and dithioperoxy ester **12** $[\alpha]_D^{25}$ − 27.4 (c 4.1 in CH_2Cl_2).
Spectral data of **12** (deduced from the spectra of the mixture of **11** and **12**): ^{1}H-NMR ($CDCl_3$): δ 2.15 (s, 3H, O=C–CH_3), 2.21 (s, 3H, S–CH_3), 6.06 (s, 1H, Ph–CH), 7.23–7.35 (m, 5H, Ph) ppm. IR (KBr): ν 1750 (s, O=C), 1725 (s, O=C–S–S–Me), 1210 (s, O=C–O) cm^{-1}. MS (CI) *m/z*: 257 (M^+ + 1), 197 [M^+ –CH_3–C(=O)–O^-], 149 [Ph–CH–O–C(=O)–CH_3, 100%], 43 (CH_3C=O^+). CI/HRMS *m/z*: 257.0306 ±0.0010 [calcd. for $C_{11}H_{13}O_3S_2$ (M^+ + 1): 257.03061].
Spectral data of **11** (deduced from the spectra of the mixture of **11** and **12**): ^{1}H-NMR ($CDCl_3$): δ 2.15 (s, 3H, O=C–CH_3), 2.28 (s, 3H, S–CH_3), 6.21 (s, 1H, Ph–CH), 7.23–7.35 (m, 5H, Ph) ppm. IR (KBr): ν 1750 (s, O=C–), 1692 (s, O=C–S–Me), 1210 (s, O=C–O) cm^{-1}. MS (CI) *m/z*: 225 (M^+ + 1), 149 (Ph–CH–O–C(=O)–CH_3, 100%), 43 (CH_3C=O^+). CI/HRMS *m/z*: 225.05854 ±0.00088 [calcd. for $C_{11}H_{13}O_3S$ (M^+ + 1): 225.05854].

(4R,5S)-3-(2-Phenylpropanoyl)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (**13a**) *and* (**13b**)

Dicyclohexylcarbodiimide (5.89 g, 73.3 mmol, 1.1 equiv.) was added to a solution of (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (MPOT)[19,20] (**15**, 12.85 g, 66.7 mmol), racemic 2-phenylpropanoic acid (10.0 g, 66.7 mmol) and 4-(dimethylamino)pyridine (DMAP) (0.81 g, 6.7 mmol) in dichloromethane (50 ml) at room temperature. After stirring for 15 h, the reaction mixture was concentrated *in vacuo* and then dissolved in ethyl acetate. The precipitate formed was removed by filtration and washed with ethyl acetate (3×25 ml). The filtrate was concentrated *in vacuo* to give 24.61 g of a crude product. The diastereomers formed were separated by column chromatography (silica gel 60H, petroleum-ether (60–80°C)/diethyl ether, 4/1, v/v) to give 9.14 g (42%) of one diastereomer (**13a**). Further elution afforded 7.45 g (35%) of the other diastereoisomer (**13b**). The absolute configuration at C-2 in **13a** and **13b** was not determined. The d.e. of both compounds exeeded 95% as determined by ^{1}H-NMR spectroscopy.
Diastereoisomer **13a**: ^{1}H-NMR ($CDCl_3$): δ 1.00 (d, 3H, *J* 6.5 Hz, C_4–CH_3), 1.60 (d, 3H, *J* 6.5 Hz, Ph–CH–CH_3), 4.63–5.03 (m, 1H, C_4–H), 5.50 (d, 1H, *J* 7.5 Hz, C_5–H), 6.15 (q, 1H, *J* 6.5 Hz, Ph–CH–CH_3), 7.13–7.60 (m, 10H, 2 Ar) ppm. IR (CCl_4): ν 1695 (s, O=C–N), 1450 (m, S=C–N), 1180 (m, S=C–N) cm^{-1}.
Diastereoisomer **13b**: ^{1}H-NMR ($CDCl_3$) δ 0.73 (d, 3H, *J* 6.5 Hz, C_4–CH_3), 1.57 (d, 3H, *J* 6.5 Hz, Ph–CH–CH_3), 4.80–5.17 (m, 1H, C_4–H), 5.67 (d, 1H, *J* 7.5 Hz, C_5–H), 6.15 (q, 1H, *J* 6.5 Hz, Ph–CH–CH_3), 7.00–7.50 (m, 10H, 2 Ar) ppm. IR (CCl_4): ν 1695 (s, O=C–N), 1450 (m, S=C–N), 1180 (m, S=C–N) cm^{-1}.

(R)-S-*Ethyl 2-phenylpropanethioate* (**14a**)

A catalytic amount of sodium hydride (0.01 g, 0.42 mmol) was added to a well-stirred solution of ethanethiol (3.50 g, 4.16 ml, 28.1 mmol) in dry THF (50 ml). To this suspension was added MPOT derivative **13a** (9.14 g, 28.1 mmol) dissolved in THF (10 ml). After the reaction mixture was stirred for 1 h it was concentrated *in vacuo*. Hexane was added to the residue and (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (MPOT) precipitated. This was removed by filtration to give 4.6 g (85%) of MPOT. The filtrate was concentrated *in vacuo* and purified by column chromatography (silica gel 60H, petroleum-ether (60–80°C)/ethyl acetate, 3:1, v/v) to give 5.0 g (92%) of **14a**, as an oil. $[\alpha]_D^{25}$ − 104.4 (c 5.80, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 1.15 (t, 3H, *J* 7.5 Hz, –S–CH_2–CH_3), 1.50 (d, *J* 6.5 Hz, 3H, Ph–CH–CH_3), 3.83 (q, 2H, *J* 7.5 Hz, –S–CH_2–CH_3), 4.78 (q, 1H, *J* 6.5 Hz, Ph–CH–CH_3), 7.30 (s, 5H, Ar) ppm. IR (CCl_4): ν 2930 (s), 1680 (s, –S–C=O), 1000 (m), 950 (s) cm^{-1}. MS (EI) *m/z*: 194 (M^+), 133 [PhCH(CH_3)C=O^+], 105 [PhCH(CH_3)$^+$].

(R)-S-*Ethyl 2-phenylpropanedithioate* (**16a**)

A solution of **14a** (5.0 g, 25.8 mmol) and Lawesson's reagent (6.25 g, 0.6 equiv., 15.5 mmol) in dry toluene (75 ml) was heated under reflux for 22 h. After cooling to room temperature, the volatiles were evaporated *in vacuo* and the residue was purified by column chromatography (silica gel 60H, petroleum-ether (60–80°C)/diethyl ether, 95/5, v/v) to give 5.08 g (94%) dithio ester **16a**, as an oil; $[\alpha]_D^{25}$ − 5.50 (c 5.84, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 3H, *J* 6Hz, –S–CH_2–CH_3), 1.70 (d, *J* 7.5 Hz, 3H, Ph–CH–CH_3), 3.07 (q, 2H, *J* 6Hz, –S–CH_2–CH_3), 4.60 (q, 1H, *J* 7.5 Hz, Ph–CH–CH_3), 7.00–7.53 (m, 5H, Ar) ppm. IR (CCl_4): ν 2920 (s), 2870 (s), 1600 (m), 1165 (s, C=S), 1100 (s), 1025 (s), 970 (s), 900 (vs) cm^{-1}. MS (EI) *m/z*: 210 (M^+), 149 [PhCH(CH_3)C=S^+], 105 [PhCH(CH_3)$^+$].

(E/Z) (1-Phenylethyl)(ethylthio)sulfine (**17**)

Starting from optically active dithio ester **16a** (2.0 g, 9.5 mmol) and *m*-CPBA (2.2 g, 1.0 equiv., 70–75% pure, 95 mmol), sulfine **17** was synthesized according to the procedure used for sulfine **2**. The crude product was purified by column chromatography (silica gel 60, petroleum-ether (60–80°C)/ethyl acetate, 3/1, v/v) to give 1.44 g (66%) of sulfine **17**, as an oil. $[\alpha]_D^{25}$ = +0.072 (c = 13.95, $CHCl_3$), immediately after its synthesis. *Z*-isomer. ^{1}H-NMR ($CDCl_3$) (deduced from the spectra of the *E/Z* mixture): δ 1,18 (t, 3H, *J* 7.5Hz, –S–CH_2–CH_3), 1.57 (d, 3H, *J* 7.5 Hz, Ph–CH–CH_3), 3.30 (q, 2H, *J*

7.5 Hz, $-S-CH_2-CH_3$), 4.00 (q, 1H, *J* 7.5 Hz, Ph-C*H*-CH_3), 7.07–7.55 (m, 5H, Ar) ppm.
E-isomer. ^{1}H-NMR ($CDCl_3$) (deduced from the spectra of the *E*/*Z* mixture): δ 1,18 (t, 3H, *J* 7.5Hz, $-S-CH_2-CH_3$), 1.57 (d, 3H, *J* 7.5Hz, Ph-CH-CH_3), 2.57 (q, 2H, *J* 7.5 Hz, $-S-CH_2-CH_3$), 5.42 (q, 1H, *J* 7.5 Hz, Ph-C*H*-CH_3), 7.07–7.55 (m, 5H, Ar) ppm. IR (CCl_4): ν 2920 (m), 1410 (s), 1270 (s), 1240 (s, C=S), 1090 (s, C=S=O), 1060 (s, C=S=O), 890 (s) cm^{-1}. MS (EI) *m/z:* 226 (M^+), 178 (M^+ –SO), 105 [$PhCH(CH_3)^+$]. EI/HRMS *m/z:* 226.04835 ±0.00088 [calcd. for $C_{11}H_{14}OS_2$ (M^+): 226.04861].

Rearrangement of sulfine **17**. A solution of sulfine **17**(0.805 g, 3.6 mmol) in dichloromethane (25 ml), while protected from light, was stirred for 1 month. Then the volatiles were evaporated *in vacuo* and the residue was purified by column chromatography (silica gel 60H, petroleum-ether (60–80°C)/ethyl acetate, 3/1, v/v) to give three fractions; *i S*-ethyl ester **14** (0.196 g, 28%) as an oil; *ii* dithioperoxy ester **18** as an oil (0.246 g, 31%), *iii* sulfinate **19** (0.150 g, 10%) as an oil. The spectral data of compound **14** thus obtained are in excellent agreement with the data of **14** obtained as described above.
18. ^{1}H-NMR ($CDCl_3$): δ 1.15 (t, 3H, *J* 7 Hz, $S-CH_2-CH_3$), 1.47 (d, 3H, *J* 6.5 Hz, Ph-CH-CH_3), 2.60 (q, 2H, *J* 7Hz, $-S-CH_2-CH_3$), 4.00 (q, 1H, *J* 6.5 Hz, Ph-C*H*-CH_3), 7.23 (s, 5H, Ar) ppm. ^{13}C-NMR ($CDCl_3$): δ 14.6 (q, $SCH_{2C}H_3$), 18.5 (q, Ph-CH-CH_3), 23.6 (t, SCH_2CH_3), 54.3 (d, Ph-CH-CH_3), 127.5 (d, Ph), 128 (d, Ph), 128.7 (d, Ph), 141.3 (s, Ph), 206.3 (C = O) ppm. IR (CCl_4): ν 2980 (s), 1723 (vs, S-S-C=O), 1453 (m), 923 (vs) cm^{-1}. IR (CS_2): ν 921 (vs), 785 (vs), 765 (s), 4.65 (vs) cm^{-1}. MS (EI) *m/z:* 226 (M^+), 165 [$PhCH(CH_3)C(O)S^+$], 133 [$PhCH(CH_3)C{=}O^+$], 105 [$PhCH(CH_3)^+$]. MS (CI) *m/z:* 227 ($M^+ + 1$), 133 (M^+ –SSEt), 105 (Ph-CH-CH_3^+, 100%). CI/HRMS *m/z:* 227.05656 ±0.00088 [calcd. for $C_{11}H_{15}OS_2$ ($M^+ + 1$): 227.05643].
19. ^{1}H-NMR ($CDCl_3$): δ 1.29 (t, 6H, *J* 7.3 Hz, $-S-CH_2-CH_3$), 1.99 (s, 6H), 3.17 (q, 2H, *J* 7.3 Hz, $-S-CH_2-CH_3$), 3.2 (q, 2H, *J* 7.3 Hz, $-S-CH_2-CH_3$), 7.2–7.6 (m, 10H). ppm. ^{13}C-NMR ($CDCl_3$): δ 11.7 (q, $SCH_{2C}H_3$), 30.1 (q, C=C-CH_3), 32.3 (t, SCH_2CH_3), 126.0 (d, Ph), 127.8 (d, Ph), 128.2 (d, Ph), 128.6 (s, Ph), 133.1 (s, C=C), 144.3 (s, C=C) ppm. IR (CCl_4): ν 3380 (br, m), 3080, 3060, 3030, 2980 (s), 2930 (s), 1450 (s), 1350 (s), 1135 (s), 1085 (s), 1055 (vs), 915 (vs) cm^{-1}. MS (CI) *m/z*: 435 ($M^+ + 1$), 419 (M^+ –O), 209 [$Ph(CH_3)C{=}C(SEt)S^+$]. CI/HRMS *m/z:* 435.0947 ±0.0017 [calcd. for $C_{22}H_{27}OS_4$ ($M^+ + 1$): 435.0946].

Photolysis of sulfine **17**. A solution of sulfine **17** (0.500 g, 2.2 mmol) in tetrachloromethane (500 ml) was irradiated at 300 nm for 2.5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel 60H, petroleum-ether (60–80°C)/ethyl acetate, 3/1, v/v) to give 0.309 g (72%) of *S*-ethyl ester **14** as an oil. The spectral data of compound **14** thus obtained are in excellent agreement with those of **14** obtained as described above.

Tert-*butyl(ethylthio)sulfine* (**21a**)

Starting from dithio ester[28] **20a** (1.55 g, 9.6 mmol) and *m*-CPBA (2.2 g, 75% pure, 9.6 mmol), sulfine **21a** was synthesized according to the procedure used for sulfine **2**. The crude product was purified by column chromatography (silica gel 60, petroleum-ether (60–80°C)/ethyl acetate, 3/1, v/v, R_f 0.27) to give 1.52 g (89%) of **21a**, in the *Z* form, as a yellow oil. ^{1}H-NMR (in $CDCl_3$): δ 1.33 [s, 9H, $C(CH_3)_3$)] 1.43 (t, 3H, *J* 7.5 Hz, CH_2-CH_3), 3.53 (q, 2H, *J* 7.5Hz, $S-CH_2-$) ppm. IR (CCl_4): ν 1140, 1060 (C=S=O), 2970, 2930, 2900, 2870 (C–H) cm^{-1}. MS (EI) *m/z:* 178 (M^+), 161, 130, 101 [$(CH_3)_3C{=}S$, 100%], 57 [$(CH_3)_3C^+$)] MS (CI) *m/z:* 179 ($M^+ + 1$), 117 [M^+ –SCH_2CH_3), 101 [$(CH_3)_3C{=}S$], 57 [$(CH_3)_3C^+$, 100%].

Rearrangement of sulfine **21a**. A solution of sulfine **21a** (0.200 g, 1.12 mmol) in dichloromethane (20 ml) protected from light was heated under reflux. After 8 h the volatiles were removed *in vacuo* to give 0.200 g (100%) of 2,2-dimethylpropanedithioperoxy acid ethyl ester **22a**. ^{1}H-NMR (in CCl_4): δ 1.20 (t, 3H, *J* 7.5 Hz, CH_2-CH_3), 1.30 (s, 9H, $C(CH_3)_3$)], 2.63 (q, 2H, *J* 7.5 Hz, $S-CH_2-$) ppm. IR (CCl_4): ν 1700 (–S–S– C=O), 2965, 2925, 2900, 2870 (C-H), 925 cm^{-1}.
Modified conditions: A solution of sulfine **21a** (0.200 g, 1.12 mmol) in dichloromethane (20 ml) protected from light, was stirred at room temperature. After 6 months the volatiles were removed *in vacuo*, to give (*E*)- and (*Z*)-(*tert*-butyl)(ethylthio)sulfine in a ratio of 1/1 as an oil. No rearranged product was isolated. *Z* Isomer. The spectral data obtained are in excellent agreement with those of the *Z* isomer obtained as described above. *E* Isomer. ^{1}H-NMR ($CDCl_3$): δ 1.33 [s, 9H, $C(CH_3)_3$], 1.43 (t, 3H, *J* 7.5 Hz, CH_2-CH_3), 2.73 (q, 2H, *J* 7.5 Hz, $S-CH_2-$) ppm. IR(CCl_4): ν 1140, 1060 (C=S=O), 2970, 2930, 2900, 2870 (C–H) cm^{-1}.
With radical scavenger. A solution of sulfine **21a** (0.200 g, 1.12 mmol) and scavenger **23** (50 mg, 0.13 mmol) in dichloromethane (20 ml) protected from light was heated under reflux. After 48 h the reaction mixture was cooled to room temperature and the volatiles were removed *in vacuo*. The residue consisted of (*E*)- and *Z*-(*tert*-butyl) (ethylthio)sulfine in a ratio of 1/1; no rearrangement was observed.

2-Propyl(methylthio)sulfine (**21b**)

Starting from dithio ester[29] **20b** (2.01 g, 15 mmol) and *m*-CPBA (3.43 g, 75% pure, 15 mmol), sulfine **21b** was synthesized according to the procedure used for sulfine **2**. The crude product was purified by column chromatography (silica gel 60, petroleum-ether (60–80°C)/ethyl acetate, 3/1, v/v) to give 1.92 g (85%) of **21b**, in an *E*/*Z* ratio of 1/2.
E-Isomer. ^{1}H-NMR ($CDCl_3$) δ 1.23 (d, 6H, *J* 7 Hz, CH_3-C-CH_3), 2.82 (s, 3H, $-S-CH_3$), 4.1 [septet, 1H, *J* 7 Hz, $(CH_3)_2C-H$] ppm. IR (CCl_4): ν 1140, 1090 (C=S=O) cm^{-1}.
Z-Isomer. ^{1}H-NMR ($CDCl_3$): δ 1.23 (d, 6H, *J* 7 Hz, CH_3-C-CH_3-), 2.45 (s, 3H, $-S-CH_3$), 4.1 [septet, 1H, *J* 7 Hz, $(CH_3)_2C-H$] ppm. IR (CCl_4): ν 1140, 1090 (C=S=O) cm^{-1}.

2-Methylpropanedithioperoxy acid methyl ester (**22b**)

A solution of sulfine **21b** (0.200 g, 1.33 mmol) in dichloromethane (20 ml) protected from light, was stirred at room temperature for 24 h. The volatiles were removed *in vacuo*, to give 0.200 g (100%) of dithioperoxy ester **22b**. ^{1}H-NMR (in $CDCl_3$): δ 1.30 (d, 6H, *J* 7.5 Hz, CH_3-C-CH_3-), 2.40 (s, 3H, $S-CH_3$), 2.88 (septet, 1H, *J* 7.5 Hz, $(CH_3)_2C-\underline{H}$) ppm. IR (CCl_4): ν 1718 (–S–S–C=O) cm^{-1}. MS(CI) *m/z:* 151 ($M^+ + 1$), 71 [$(CH_3)_2CHCH{=}O^+$, 100%]. CI/HRMS *m/z:* 151.02514 ±0.00088 [calcd. for $C_5H_{11}O_2S_2$ ($M^+ + 1$): 151.02513].
Modified conditions: A solution of sulfine **21b** (0.200 g, 1.33 mmol) and scavenger **23** (50 mg, 0.13 mmol) in dichloromethane (20 ml) protected from light, was stirred at room temperature for 96 h. The volatiles were removed *in vacuo*, to give 0.200 g (100%) of dithioperoxy ester **22b**.

Acknowledgements

This investigation was supported by the Netherlands Foundation of Chemical Research with financial aid from the Netherlands Organization for Scientific Research (NWO). We thank Dr. *H.J.G. Broxterman* for stimulating discussions and his assistance in preparing the manuscript.

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